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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,091	12/21/2001	Holly Hogrefe	25436/2152	1719

27495 7590 06/18/2003

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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/18/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/035,091	Applicant(s) HOGREFE ET AL.	
	Examiner Richard G Hutson	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-14,20-26 and 30-35* is/are pending in the application.

4a) Of the above claim(s) *23-26 and 30-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-14 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,11,13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-3, 6-14, 18, 20-26, and 30-35 are still at issue and are present for examination. It is noted that applicants previous amendment included the cancellation of claim 9, followed by an amendment of claim 9. As claim 9 was cancelled, claim 9 could not be amended as per the previous amendment. For the sake of advancing prosecution, claim 9 has been examined below as if applicant's mistakenly cancelled claim 9, prior to its amendment. Applicants should note this and amend the claims accordingly.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-3, 6-14, 18 and 20-22 in Paper No. 16 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 23-26 and 30-35 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

It is acknowledged that no statements claiming earlier priority then that of the filing date of the instant application, 12/21/2001, have been made by applicants.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Applicants filing of information disclosures, Paper No. 3, filed 3/29/2002, and Paper No. 11, filed 11/25/2002, and Paper No. 13, filed 12/23/2002, are acknowledged. Those references considered have been initialed.

Specification

The disclosure is objected to because of the following informalities:

On page 2, line 20, applicants refer to U.S. Patent No. 6,008,205 as disclosing methods for improving DNA amplification fidelity. U.S. Patent No. 6,008,205 is directed to presqualene diphosphate (PSDP) analogs having an active region of natural PSDP and a metabolic transformation region resistant to rapid intracellular inactivation in vivo, and therefore its relevance to the instant application is questioned.

Appropriate correction is required.

Claim Objections

Claims 7 is objected to because of the following informalities:

Claim 7 recites "...said first enzyme is Archaeal DNA polymerase..." This should be "...said first enzyme is **an** Archaeal DNA polymerase..."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 9, 10, 11-14, 20- 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (2-3, 10, 11, dependent on), 9, 12 (13, 14, 20, 22 dependent on) 21are indefinite in that the recitation "... a mutant *Pfu* DNA polymerase comprising one or more mutations at amino acid positions selected from the group consisting of: D405, Y410, T542, D543, K593, Y595, Y385, G387 and G388..." is unclear. Specifically it is unclear in the recitation "one or more mutations" if it is applicants intent to claim a mutant *Pfu* DNA polymerase wherein said mutant *Pfu* DNA polymerase consists of mutations at positions D405, Y410, T542, D543, K593, Y595, Y385, G387 and G388 or if it is applicants intent to claim a mutant *Pfu* DNA polymerase wherein said mutant *Pfu* DNA polymerase consists of mutations at positions D405, Y410, T542, D543, K593, Y595, Y385, G387 and G388 or additional mutations that result in maintaining the 3'-5' exonuclease activity and a reducing or diminishing DNA polymerization activity. For the sake of advancing prosecution the above recitation is interpreted as if it is applicants

intent to claim "... a mutant *Pfu* DNA polymerase comprising one or more mutations, **wherein said mutation(s) are selected from** amino acid positions selected from the group consisting of: D405, Y410, T542, D543, K593, Y595, Y385, G387 and G388"

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 7, 8, 18 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 6, 7, 8, 18 and 20 are directed to all possible enzyme mixtures and kits comprising said enzyme mixtures, comprising a first enzyme that is an Archael DNA polymerase and a second enzyme that is any mutant Archael DNA polymerase comprising a 3'-5' exonuclease activity and a reduced DNA polymerization activity (claims 7, 18 and 20), wherein said mutant DNA polymerase is derived from U1Tma DNA polymerase, Tli DNA polymerase, Pfu DNA polymerase, KOD DNA polymerase, JDF-3 DNA polymerase, PGB-D DNA polymerase and DP1/DP2 DNA polymerase, wherein said enzymes are derived Pfu and mutant Pfu DNA polymerases (claims 6 and 8). The specification, however, only provides those enzyme mixtures encompassed by these claims, wherein said enzyme mixture comprises a Archael DNA polymerase and a mutant Pfu polymerase comprising a 3'-5' exonuclease activity and a reduced DNA

polymerization activity wherein said mutant Pfu polymerase comprises a mutation at D405, Y410, T542, D543, K593, Y595, Y385, G387 or G388 of Pfu DNA polymerase. There is no disclosure of any particular structure to function/activity relationship in the disclosed species that would put one in possession of the genus of mutations of Pfu DNA polymerase that would result in maintaining 3'-5' exonuclease activity and a reduced DNA polymerization activity. The specification also fails to describe additional representative species of these mutant enzymes by any identifying structural characteristics or properties other than the activities recited in claims 6, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 6, 7, 8, 18 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enzyme mixture comprising a first enzyme which comprises a DNA polymerization activity and a second enzyme which is a mutant Pfu DNA polymerase, wherein said mutant Pfu polymerase comprises a mutation at D405, Y410, T542, D543, K593, Y595, Y385, G387 or G388 of Pfu DNA polymerase, does not reasonably provide enablement for an enzyme mixture

comprising a first enzyme which comprises a DNA polymerization activity and a second enzyme wherein said second enzyme comprises any enzyme which comprises a 3'-5' exonuclease activity and a reduced DNA polymerization activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 6, 7, 8, 18 and 20 are so broad as to encompass any enzyme mixture and kit comprising said enzyme mixture, comprising a first enzyme that is an Archael DNA polymerase and a second enzyme that is any mutant Archael DNA polymerase comprising a 3'-5' exonuclease activity and a reduced DNA polymerization activity (claims 7, 18 and 20), wherein said mutant DNA polymerase is derived from U1Tma DNA polymerase, Tli DNA polymerase, Pfu DNA polymerase, KOD DNA polymerase, JDF-3 DNA polymerase, PGB-D DNA polymerase and DP1/DP2 DNA polymerase (claim 8), wherein said enzymes are derived Pfu and mutant Pfu DNA polymerases (claims 6). The scope of the claims is not commensurate with the enablement provided

by the disclosure with regard to the extremely large number of mutant DNA polymerase enzymes broadly encompassed by the claimed mixtures and kits, including any mutant Archael DNA polymerase comprising a 3'-5' exonuclease activity and a reduced DNA polymerization activity and variants thereof. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the claimed mutant DNA polymerases. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to those instantly disclosed mutant Pfu DNA polymerases comprising a 3'-5' exonuclease activity and a reduced DNA polymerization activity.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any mutant Archael DNA polymerase comprising a 3'-5' exonuclease activity and a reduced DNA polymerization activity, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting 3'-exonuclease activity while causing a reduction in polymerizing activity; (B) the general tolerance of Archael DNA polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of any Archael DNA polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the 3'-5' exonuclease activity while reducing or diminishing the polymerase activity, claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those mutant Archael DNA polymerases of the claimed genus having the claimed activities.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including those enzyme mixtures comprising any

mutant Archael DNA polymerase comprising a 3'-5' exonuclease activity and a reduced DNA polymerization activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 3, 8 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention of claims 3, 8 and 14 appear to employ DNA polymerases from novel strains of bacterium. Since the polymerases, U1Tma DNA polymerase, Tli DNA polymerase, JDF-3 DNA polymerase, PGB-D DNA polymerase and DP1/DP2 DNA polymerase are essential to the claimed enzyme mixtures and kits, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The DNA polymerases are not fully disclosed, nor have they been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the DNA polymerases or the bacterium from which they are isolated. Accordingly, it is deemed that a deposit of these

polymerases or bacterium should have been made in accordance with 37 CFR 1.801-1.809.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 7, 8, 10-14, 18, 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnes et al. (U.S. Patent No. 5,436,149) and Komori et al. (Protein Engineering, Vol 13. No. 1, pages 41-47, 2000).

Barnes teach a number of thermostable DNA polymerase mutants and formulations of the taught DNA polymerases and other thermostable DNA polymerases, which formulation of enzymes are capable of efficiently catalyzing the amplification by PCR of unusually long and faithful DNA products. Barnes specifically teach a formulation of thermostable DNA polymerases comprising at least one thermostable DNA polymerase lacking 3'-exonuclease activity and at least one thermostable DNA polymerase exhibiting 3'-exonuclease activity, wherein the thermostable DNA polymerase exhibiting 3'-exonuclease activity is a variant of the *Pfu* DNA polymerase wherein the DNA polymerase activity of said *Pfu* DNA polymerase has been diminished or inactivated.

Komori et al. teach the functional interdependence of DNA polymerizing and 3'-5' exonucleolytic activities in *Pyrococcus furiosus* (*Pfu*) Polymerase I. Specifically, Komori et al teach a number of *Pfu* DNA polymerase mutants which affect both the DNA polymerizing and/or the 3'-5' exonucleolytic activity in varying amounts. Komori et al. specifically teach mutant *Pfu* DNAS polymerases in which the Asp 405 has been replaced by alanine, D405A, and glutamate, D405E. Each of these mutants have a greater then 100-fold and greater then 20-fold decrease, respectively, in the polymerizing activity of the mutant DNA polymerase, relative to the wildtype *Pfu* DNA polymerase. These mutants further have an approximate 10-fold decrease in the exonuclease activity. Thus each of the mutants created by Komori et al. have an approximate 50-fold and 2-fold increase, respectively, in the ratio of 3'-exonucleolytic activity to polymerizing activity relative to the wildtype *Pfu* DNA polymerase.

One of ordinary skill in the art at the time of filing would have been motivated to use either of the *Pfu* DNA polymerase mutants, D405A and D405E, taught by Komori et al. in the formulation taught by Barnes et al. to catalyze the amplification by PCR of unusually long and faithful DNA products. One would have been further motivated to include in the above formulation a PCR enhancing factor or an additive, as the purpose of the taught formulation is for PCR and package this formulation as a kit. The motivation for using the *Pfu* DNA polymerase mutants taught by Komori et al. comes from Barnes who teach that the thermostable DNA polymerase exhibiting 3'-exonuclease activity of the DNA polymerase formulation is preferably a variant of the *Pfu* DNA polymerase, wherein the DNA polymerase activity of said *Pfu* DNA

polymerase has been diminished or inactivated. The mutants taught by Komori et al. are such variants of the *Pfu* DNA polymerase, wherein the DNA polymerase activity of said *Pfu* DNA polymerase has been diminished or inactivated. The reasonable expectation of success is high as both Barnes and Klomori et al. teach a number of thermostable DNA polymerases for use in the taught formulation, and Komori et al. specifically teach the *Pfu* DNA polymerase, wherein the DNA polymerase activity of said *Pfu* DNA polymerase has been diminished or inactivated. It is acknowledged that the mutant *Pfu* DNA polymerases taught by Komori et al. in addition to having a diminished or inactivated DNA polymerase activity also have a reduced 3'- exonucleolytic activity, however as the specific mutants taught by Komori et al. actually have an increase in the ratio of 3'-exonucleolytic activity to DNA polymerizing activity, they would remain useful in the formulation of Barnes, as the presence of the 3'-exonucleolytic activity is the reason for addition of the second DNA polymerase of the formulation. This is further supported by the teachings and claims of Barnes who teach that the ratio of the "polymerase without 3'-exonucleolytic activity" to the "polymerase with 3'-exonucleolytic activity, wherein the polymerase activity is reduced or diminished" is high (i.e. from 10 to 2000 units to 1 unit), suggesting that the only functional property of the second polymerase that is important is the presence of the 3'-exonucleolytic activity, and that based on the ratios of the taught polymerase formulations, a slight decrease in the level of 3'-exonucleolytic activity can be accounted for by adjusting the ration of polymerases to remain within the level suggested by Barnes.

Thus claims 1-3, 7, 8, 10-14, 18, 20-22 are made obvious over Barnes et al. and Komori et al.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-3, 6, 9-14, 18 and 20-22 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-3, 6, 9-11, 13-15, 19 and 21-23 of copending Application No. 10/079,241. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned

are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
June 16, 2003